December 10, 2002

Timothy Adams, Ph.D.
Technical Contact
The Flavor and Fragrance High Production Volume Consortia
1620 I Street, N.W.
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Washington D.C. 20006

Dear Dr. Adams:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Benzyl Derivatives category posted on the ChemRTK HPV Challenge Program Web site on January 31, 2002. I commend the Aromatic Consortium of the Flavor and Fragrance High Production Volume Consortia (FFHPVC) for its commitment to the HPV Challenge Program.

The FFHPVC noted in its test plan that all ten of the sponsored substances are listed by the U.S. Food and Drug Administration (FDA) as Generally Recognized as Safe (GRAS). FDA publicly available files may contain toxicity information to support the submission; especially for the developmental toxicity endpoint.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the FFHPVC advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the “Contact Us” link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
W. Penberthy
A. Abramson
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Benzyl Derivatives Category

SUMMARY OF COMMENTS

The sponsor, the Aromatic Consortium of the Flavor and Fragrance High Production Volume Consortia, submitted a test plan and robust summaries for the benzyl derivatives category to EPA dated December 26, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 31, 2002. The category consists of ten substances identified below under "Category Definition."

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. EPA considers the proposed category approach reasonable for health effects endpoints and environmental fate endpoints, but not for ecological effect endpoints. Existing and/or estimated physicochemical data are available for all substances, so a category approach is not necessary for these endpoints.

2. Physicochemical Properties and Environmental Fate. (a) Hydrolysis tests need to be run for benzyl acetate and methyl 2-hydroxybenzoate. (b) Additional studies for melting point, water solubility, and biodegradation were found during review and should be added to the robust summaries and test plan.

3. Health Effects. All appropriate SIDS-level endpoints, except developmental toxicity, have been addressed for the purposes of the HPV Challenge Program.

4. Ecological Effects. EPA believes it is necessary to divide these chemicals into three subcategories (esters only, aldehydes only, and ester/phenols) and one single chemical (aldehyde/phenol; CAS No. 121-33-5) and treat each group separately. Data on several chemicals lack sufficient robust summary information to make an independent data adequacy evaluation; therefore, the missing robust summary data elements need to be provided. (All algal data submitted are inadequate for the purposes of the HPV Challenge Program.) EPA agrees with the submitter's proposal of acute toxicity tests in daphnia and algae, but also believes additional testing is necessary.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON BENZYL DERIVATIVES CHALLENGE SUBMISSION

Category Definition

The proposed chemical category includes the following ten substances:

Benzaldehyde	CAS No. 100-52-7
p-Methoxybenzaldehyde	CAS No. 123-11-5
m-Methoxy-p-hydroxybenzaldehyde	CAS No. 121-33-5
Benzyl acetate	CAS No. 140-11-4
Benzyl benzoate	CAS No. 120-51-4
Methyl benzoate	CAS No. 93-58-3
Methyl p-methylbenzoate	CAS No. 99-75-2
Methyl 2-hydroxybenzoate	CAS No. 119-36-8
Pentyl 2-hydroxybenzoate	CAS No. 2050-08-0
Benzyl 2-hydroxybenzoate	CAS No. 118-58-1

These ten substances are further subdivided into three subcategories: benzaldehyde derivatives (benzaldehyde, p-methoxy, and m-methoxy-p-hydroxybenzaldehyde); two benzyl (benzyl acetate and benzyl benzoate) and two benzoate (methyl benzoate and methyl p-methylbenzoate) esters; and three 2-hydroxybenzoate esters (methyl, pentyl, and benzyl 2-hydroxybenzoate). The category definition is clear and unambiguous.

Category Justification

The submitter included the ten substances in the same category because they all contain a substituted or unsubstituted benzene ring bonded directly to a single oxygenated carbon. The submitter expects the toxicologic properties of the members of the category to be similar because of the formation of similar stable metabolites, i.e., benzoic acid derivatives corresponding to the category members. The overall argument of an alcohol >> aldehyde >> acid "metabolism train" is a widely accepted pharmacokinetic principle. Therefore, for health effects the approach is, in general, reasonable. EPA notes that the test plan provides details on many adsorption, distribution, metabolism, and excretion studies on three of the sponsored substances and eleven non-sponsored substances. However, most of the experiments are summarized in two or three sentences, and the connection between the non-sponsored substances and sponsored substances is not stated.

For ecological effects, EPA agrees with the submitter that all the members of the category are structurally similar in that they all contain an aromatic ring bonded directly to an oxygenated carbon. However, the substituents and functional groups are different enough that the phenols, aldehydes, and esters could each show different toxicities and species sensitivities. Furthermore, the combined effects of multiple functional groups on aquatic toxicity are unknown. The submitter may wish to reconsider its category approach on this basis.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility)

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program. However, EPA identified existing data for compounds for which the submitter provided only calculated data. These should be added to the test plan and appropriate robust summaries provided.

Melting Point. EPA located measured melting point values for CAS Nos. 2050-08-0 and 118-58-1 in the Beilstein Online database, Hawley's Condensed Chemical Dictionary, and Chemfinder. This information should be added to the test plan and robust summaries (to show that all ten substances have measured data).

Vapor Pressure. The test plan and robust summaries should be corrected to state that measured vapor pressure data are available for eight of the ten substances.

Water Solubility. A measured water solubility value was found for CAS No. 99-75-2 in the Beilstein Online database. This information should be added to the test plan and robust summaries to show that measured data are available for seven of the ten compounds.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

Stability in water. Hydrolysis tests are needed for CAS Nos. 140-11-4 and 119-36-8. Some of the literature data for CAS No. 140-11-4 indicate persistence while other data show hydrolysis rates that are environmentally significant. Reported hydrolysis half-lives at pH 7 range from 38 days to 118 years, indicating that an additional study is needed to clarify the importance of hydrolysis.

The literature value for CAS No. 119-36-8 is substantially lower than the lowest estimated half-life and was measured at a higher pH. In addition, the estimated values vary widely in the pH range 7 to 8. The higher calculated values may be attributed to the lack of sensitivity of the estimation model for the presence of a 2-hydroxy group. The submitter needs to provide measured values for this substance.

Biodegradation. Measured biodegradation studies were found for CAS No. 100-52-7 in Means and Andersen (1981 and Chemicals Inspection and Testing Institute (1992). This additional information should be added to the test plan so that measured data are included for nine of the ten compounds.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for all SIDS-level health endpoints -- except developmental toxicity -- for the purposes of the HPV Challenge Program.

Acute Toxicity. The submission contained adequate acute toxicity data for all ten sponsored substances.

Repeated-Dose. The three subcategories of benzaldehydes, benzyl/benzoate esters, and 2-hydroxybenzoate esters are adequately covered for the repeated-dose endpoint for the purposes of the HPV Challenge Program.

Reproductive Toxicity. The three subcategories of benzaldehydes, benzyl/benzoate esters, and 2-hydroxybenzoate esters are adequately covered for the purposes of the HPV Challenge Program. EPA notes that some of the repeated-dose studies with benzaldehyde, benzyl acetate, and benzyl benzoate showed evidence of reproductive organ effects.

Developmental Toxicity. Because only two of the 10 substances have been adequately tested for this endpoint -- both in the benzyl/benzoate ester subcategory -- EPA believes that this endpoint has not been satisfied for the purposes of the HPV Challenge Program. At a minimum, one representative from each of the other two subcategories (benzaldehydes and 2-hydroxybenzoates) should be tested for developmental effects.

Genetic Toxicity (gene and chromosomal effects). Adequate data are available for these two endpoints for the purposes of the HPV Challenge Program.

Ecotoxicity (fish, invertebrates, algal toxicity)

EPA agrees with the submitter's plan to conduct further tests on aquatic invertebrates where indicated. However, EPA has concerns about the category approach because of the existence of different functional groups in one structure. Aquatic toxicity is relatively well characterized for phenols, esters, and aldehydes but not for substances that contain more than one of these functional groups such as is seen in this submission. EPA considers a different category approach to be more appropriate: testing the single ester base structures, single aldehyde base structures (CAS Nos. 100-52-7 and 123-11-5), and single phenol and ester base structures. In the case of CAS No. 121-33-5, the only chemical having both the aldehyde and phenol groups present, EPA believes this chemical should be examined separately for aquatic hazards.

An EPA search of in-house databases identified fish 96-hour LC50 values of 7.61 and 12.8 mg/L for benzaldehyde. EPA suggests that the sponsor use these data to satisfy this endpoint.

The algal data submitted were not produced according to a recognized test guideline method. Exposure durations of 72 or 96 hours and measured EC50 values were not achieved. In addition to testing already proposed by the submitter, EPA proposes algal testing for *m*-methoxy-*p*-hydroxybenzaldehyde to determine the effect of combined aldehyde and phenol functional groups on toxicity to algae.

EPA reserves judgment on the adequacy of the submitted fish and invertebrate studies. The submitter needs to provide critical data elements missing in the robust summaries to permit an independent evaluation of the data.

Specific Comments on the Robust Summaries

Environmental Fate

Biodegradation. The results of BIOWIN are incorrectly reported. Model output is the time expected for complete primary or ultimate degradation. The summaries indicate a general duration on the order of “weeks”, “days”, or “years”. The values in the model should not be literally interpreted as stating the actual number of weeks, days or years.

Health Effects

There were many health effects studies submitted. In general, the majority were adequate and EPA agreed with the reliability assignments made by the submitter. Deficiencies for studies deemed not reliable are not mentioned here.

Repeated-dose Toxicity. For all summaries, the study type is listed as subacute when they are clearly subchronic or chronic studies.

Reproductive Toxicity. As noted above, there is information in several repeated-dose studies that discuss effects on reproductive organs for a number of category members (benzaldehyde, benzyl acetate, and benzyl benzoate). This information is useful because the robust summaries reported under the toxicity to reproduction sections are, in general, inadequate: (a) The benzaldehyde summary is confusing. It might be better if the appropriate language from the repeated-dose studies which examined reproductive organs following subchronic benzaldehyde exposures were placed here. The sex of the test organisms is given as “male” when clearly males and females were used. Results listed under “offspring toxicity” are incomplete and appear to have been inadvertently deleted. The results further suggest that it was a two-generation study when it is called a one-generation study. (b) The two benzyl acetate studies are 90-day studies that examined reproductive organs. The sex of the test organisms is given as “male” when clearly males and females were used. (c) In the methyl salicylate studies, the sex of the test organisms is given as “male” when clearly males and females were used.

Developmental Toxicity. For all robust summaries few or no quantitative data were given, and the sex of the test species is given as “male” when clearly females were used. The benzyl benzoate study is inadequate because there were no control animals and there is no description of the method used.

Genetic Toxicity. Because of the large number of studies submitted, only selected studies were reviewed. Deficiencies in the adequate studies reviewed (primarily for benzaldehyde, benzyl alcohol, benzyl acetate and methyl 2–hydroxybenzoate) consisted primarily of not identifying the purity of the test substance or the statistical methods used.

Ecotoxicity

Fish. Adequate data are available on five members of the category. However, the submitter needs to provide critical data elements missing from three of the robust summaries.

CAS No. 121-33-5. Missing data elements on three potentially adequate studies include pH, water temperature, water hardness, DO, test conditions, number of replicates, chemical purity, and test concentrations.

CAS No. 140-11-4. Missing data elements on three potentially adequate studies include pH, water temperature, water hardness, DO, test conditions, number of replicates, chemical purity, and test concentrations.

CAS No. 93-58-3. Missing data elements needed on the 96-hour LC50 test include chemical purity, pH, DO.

Fish acute toxicity robust summaries should be developed and submitted for benzaldehyde from Brooke et al. (1984) and Geiger et al. (1985).

Invertebrates.

CAS No. 93-58-3 Missing critical data elements include chemical purity, pH, DO, water temperature, if and when the test concentrations were changed and age of the animals at test initiation

CAS No. 118-58-1. Missing data elements on three potentially adequate studies include pH, water temperature, water hardness, DO, test conditions, number of replicates, chemical purity, test concentrations, if and when the test concentrations were changed, and age of the animals at test initiation.

CAS No. 2050-08-0. The invertebrate value needs to be provided in the robust summary (it appears as 2.8 mg/L in the test plan).

Follow up Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

References

Beilstein Online database. Available at: http://www.chemweb.com/databases/beilstein/

Brooke L. T. et al. 1984. “Acute Toxicities of Organic Chemicals to Fathead Minnows (Pimephales Promelas) Vol. I, Center for Lake Superior Environmental Studies, University of Wisconsin-Superior, U.S. EPA Cooperative Agreements 806864 and 809234.

Chemfinder. Available at http://chemfinder.cambridgesoft.com/.

Chemicals Inspection & Testing Institute; Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, Ministry of International Trade & Industry, Japan, p. 3-88, 1992.

Geiger, D. L. et al. 1985. “Acute Toxicities of Organic Chemicals to Fathead Minnows (Pimephales Promelas) Vol. II, Center for Lake Superior Environmental Studies, University of Wisconsin-Superior, U.S. EPA Cooperative Agreements 806864 and 809234.

Lewis, R.J. Sr. ; Hawley’s Condensed Chemical Dictionary, 13th Edition, New York, NY: John Wiley & Sons, Inc., p. 123, 77, 1997.

Means, J.L. and Anderson, S.J.; Comparison of five different methods for measuring biodegradability in aqueous environments. Water, Air, Soil Pollut., 16: 301-315, 1981.